Applicant : Yoshihito Ikeda et al.
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REMARKS

Claim 19 has been amended. Claim 1 has also been amended to correct a typographical error. Upon entry of the above amendments, claims 1, 4, 6-8, 10-14, and 19 will remain pending and under consideration in the application.

Claim Rejections Under 35 U.S.C. §112

Claim 19 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner has objected to the phrase "rapidly reconstituteable" because the term "rapidly" is a relative term, which does not set out consistent metes and bounds for the claimed subject matter.

While the meaning of "rapidly reconstituteable" is expressly stated in the claim ("wherein the composition completely dissolves in water in less than 10 seconds"), the word "rapidly" has been deleted to expedite prosecution and conform to the Examiner's requirements.

Rejections Under 35 U.S.C. §103

All of the claims (1, 4, 6-8, 10-14, and 19) have been rejected under 35 U.S.C. §103(a) over JP 9-117279 in view of JP 1-304882.

Admittedly, the JP '279 reference discloses lecithin-modified superoxide dismutase (PC-SOD), and the JP '882 reference discloses the combination of unmodified superoxide dismutase (SOD) and at least one sugar such as ketose or sugar alcohol. Further, the JP '882 reference discloses that SOD is combined with sugar to stably store SOD in a frozen state.

The Examiner has reasoned that one having ordinary skill in the art would have been motivated to attempt to improve the storage stability of PC-SOD by combining it with a sugar, such as sucrose, based on the known use of sugar for stabilizing SOD since both PC-SOD and SOD catalyze the same chemical reaction and are useful for treating the same disorders.

While the Examiner's argument has some superficial appeal, it does not take into consideration the fact that PC-SOD and SOD degrade and lose their stability by different mechanisms, and that neither preservation of the active site nor the utility of PC-SOD and SOD

for treating similar or the same disorders are relevant to stabilizing the compounds against degradation.

As disclosed in U.S. Patent No. 4,966,774, SOD exhibits poor stability and "would suffer from clouding caused by polymerization." In contrast, the specification for the above-referenced patent application expressly states (at page 16) that degradation and loss of activity of PC-SOD occur as a result of cleavage of lecithin linked to PC-SOD. The attached Declaration of Yoshitomi Morizawa shows that PC-SOD undergoes degradation by liberation of palmitic acid from the decomposition of the lecithin (PC) unit (as illustrated in Figure 3 of the Declaration). Unmodified SOD cannot release palmitic acid during degradation, since unmodified SOD does not have PC units or any other moiety from which palmitic acid can be liberated (see paragraph 18 on page 4 of the Declaration). Thus, it is readily apparent from the evidence that unmodified SOD does not undergo degradation by the same mechanism as PC-SOD, *i.e.*, PC-SOD undergoes degradation by liberation of palmitic acid from the lecithin units, whereas SOD cannot release palmitic acid because it does not have lecithin units or any comparable structure capable of releasing palmitic acid.

To the contrary, it is reported in the literature that SOD degradation is "caused by polymerization." As indicated in the attached Declaration of Yoshitomi Morizawa, "Those having ordinary skill in the art could reasonably expect that agglomeration or polymerization of PC-SOD is not a predominant degradation mechanism due to steric hindrance and different surface functionalities caused by the PC unit" (see paragraph 21 on page 4 of the Declaration).

Thus, it is apparent that PC-SOD and SOD degrade by entirely different mechanisms, neither of which is related to its utility or active site. Because PC-SOD and SOD degrade by entirely different mechanisms, those having ordinary skill in the art would not expect that agents which are effective for preventing degradation of SOD would also be effective for preventing degradation of PC-SOD. More specifically, there is nothing in the prior art which would suggest that sugars, which apparently are effective at preventing polymerization of SOD, would also be effective at preventing degradation of the PC unit of PC-SOD.

Further, Applicants' specification shows that other stabilizing agents including alanine, inositol, mannitol, sorbitol, creatinine, glycine, polyethylene glycol, and urea are

unacceptable, especially for a drug composition that is reconsitutable from a dry form and completely dissolves in water in less than 10 seconds, either because it does not dissolve completely within 10 seconds (*e.g.*, sorbitol and creatinine) or because it does not prevent degradation of the lecithin unit (alinine, inositol, mannitol, creatinine, glycine, polyethylene glycol, and urea). Only sucrose prevents degradation of the lecithin moieties while also facilitating complete dissolution within 10 seconds (see Table 2 on page 28 of the specification).

Conclusion

In view of the above amendments and remarks, and in view of the attached Declaration of Yoshitomi Morizawa, it is respectfully submitted that stabilization against PC-SOD degradation by liberation of palmitic acid via decomposition of the lecithin moiety using sucrose would not have been obvious to one having ordinary skill in the art based on the use of sucrose to stabilize SOD against polymerization. Accordingly, a Notice of Allowance is earnestly solicited.

Respectfully submitted,

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